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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	37

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
08/366,083	POMERANTZ ET AL.
Examiner	**Art Unit**
Terry McKelvey	1636

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2001*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,24,27-30,34,36,40-70 and 72-98* is/are pending in the application.

4a) Of the above claim(s) *1-21,24,27-30,34 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-70,72-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Gita Cranes

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other

DETAILED ACTION

Election/Restriction

Claims 1-21, 24, 27-30, 34, and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 12, filed 3/19/98.

This application contains claims 1-21, 24, 27-30, 34, and 36 drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-70 and 72-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor [illegible], at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record set forth in Paper No. 33, mailed 9/21/00 and repeated below. Applicants' arguments filed 3/23/01 have been fully considered but they are not deemed to be persuasive.

The claimed invention is drawn to a nucleic acid and its use, the nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein the two nucleic acid binding domains do not occur in the same protein in nature, do not occur in the same protein in nature in the order in which they are present in the chimeric protein, or do not occur in nature with the same spacing that is present in the chimeric protein.

These are genus claims. The specification fails to disclose even one embodiment that definitively meets the claim limitations because the specification does not teach that any one embodiment is definitely not present in nature. The specification also fails to teach how one of skill in the art would know that a particular combination of nucleic acid binding domains are

[illegible]ly not found encoded in a natural gene. There is no description of what combinations of nucleic acid [illegible] a [illegible] which [illegible]y do not exist in nature. The general knowledge in the art concerning known genes and gene mutations does not provide any indication of the excluded structures of nucleic acids of natural genes that have not been identified or sequenced yet, but which are still excluded by the claim limitations. The nature of different genes in the art is that they tend to vary unpredictably and thus, unless the nucleotide sequence of the different genes are empirically determined, they are not known and not predictable. The present and foreseeable state of the art is that the structure of one or more known genes does not predict the specific structures of one or more other genes that are presently unknown. The common structural attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus, especially because there is no description of even one member of the claimed genus that definitively meets the claim limitations [illegible] it was not shown that the nucleic acid was not present in nature, and thus, the description of the claimed invention is insufficient to support the claims.

Response to Arguments

The applicant argues that the fundamental factual inquiry is whether one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention at the time it was filed. Applicants argue that the specification clearly conveys that the Applicants had possession of the subject method of the pending claims. The examiner respectfully disagrees. The claimed invention is drawn to a nucleic acid encoding a chimeric protein which comprises two nucleic acid binding domains, each of which binds a sequence which is a portion of a binding site, wherein only one of the two nucleic acid binding domains includes a zinc finger motif and wherein the two nucleic acid binding domains do not occur in the same protein in nature, do not occur in the same protein in nature in the order in which they are present in the chimeric protein or do not occur in nature with the same spacing that is present in the chimeric protein. Thus, the claimed invention is drawn to the genus of nucleic acids meeting these claim limitations, which claim limitations include a negative limitation. In order to describe the claimed genus which includes an exclusion, the exclusion part as it limits the rest of the claim must be described. If the exclusion part of the claim is not described, how can the claimed invention be

by the exclusion be described? It is clear that it can't be described when the exclusion is not described. It is also clear that the specification has no description of the proteins in nature that meet the exclusion limitation. In fact, one skilled in the art clearly knows that only a minuscule fraction of all proteins in nature that may have two or more DNA binding domains are known and that it is logically impossible to ever even come close to knowing a significant fraction of them and thus describing a nucleic acid defined by the negative limitation drawn to the extremely broad limitation of excluding all of the nucleic acids encoding proteins that have two nucleic acid binding domains as claimed that exist in nature because only a relative few of the genes encoding proteins from the six million plus species that exist and the allelic variants within each species are known at the time of filing and natural mutations in the genes encoding DNA binding proteins continue to occur and are present throughout the populations of all organisms, requiring that essentially limitless amounts of sequences be described before even a small fraction of the total are described.

In summary, in order to have a description of the claimed genus, there must be a description of the nucleic acids that are excluded from the first part of the claim <u>because the claimed</u>

invention is defined by that exclusion. The central point of the instant written description rejection is that there is no description in the specification of the broad range of nucleic acids that are excluded from the first part of the claimed invention and thus, because of the lack of description of the nucleic acids that make up the exclusion, one skilled in the art would not reasonably conclude that the inventor had possession of the claimed invention which is drawn to a genus of nucleic acids which have the exclusion limitation.

The applicant argues that one of ordinary skill in the art would reasonably believe that the various working examples of the present invention represent proteins which do not exist in nature and that the Examiner has not provided any factual basis in which an argument to the contrary could reasonably be based. This argument is not persuasive for the following reasons. First, there only appears to be one specific working example of a nucleic DNA binding protein described in the specification, [illegible], made from fingers 1 and 2 of Zif268 and the Oct-1 homeodomain. One example hardly qualifies as "various". Second, there is no description in the specification that this chimeric transcription factor actually meets all of the claim limitations, including that this protein's two nucleic acid binding domains

[illegible] in the same protein in nature, or not found in the same protein in nature in the order in which they are present in the chimeric protein or do not occur in nature with the same spacing that is present in the chimeric protein. Because one of skill in the art clearly knows that very few proteins that exist in nature are known, one of skill would recognize not only that it is not known whether the single chimeric protein example meets the claim limitations, but also that it is impossible to ever truly know whether the protein or any other protein ever meets the claim limitations. It is the inherently flawed nature of the claim limitations, which recites a negative limitation that isn't described, that necessitates the instant rejections under 35 USC 112, first paragraph. By defining the claimed invention with a negative limitation, the claim requires a description of that negative limitation in order to describe the claimed invention and thus, because the negative limitation essentially requires infinite knowledge (a knowledge of all of the proteins in nature , infinite knowledge is required to describe the claimed invention. This is the reasoning that the instant rejection relies upon. Although this reasoning may not necessarily consist of evidence as such to provide a factual basis as the applicant appears to indicate as being required for a showing of lack of

written description, this reasoning certainly qualifies as [illegible] as to why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. That is all is needed with regard to written description. In actuality, however, the reasoning presented does depend on the indisputable facts that only a minuscule fraction of all natural proteins were known at the time of filing, the specification fails to describe any of the proteins having two nucleic acid binding domains which would be excluded from the claimed invention, that it is logically impossible to ever know a significant fraction of all natural proteins having two nucleic acid binding domains, the specification fails to teach or assert that the one embodiment of a protein having two nucleic acid binding domains actually meets the limitations of the claimed invention, and that the claimed invention is drawn to nucleic acids which require a description of what is excluded.

The applicant argues that when one invents novel compounds, an applicant is not required by the description or other requirements to prove definitively that any or all of the claimed species is not found in nature and that claims to those compounds are not rejected as products of nature because they might occur in nature. The applicant asserts that similarly,

claims to assertedly novel compounds are not rejected under the description requirement on the grounds that an applicant has not disclosed all known compounds or all compounds which might occur in nature. This argument is not persuasive for the following reasons. First, the specification has not asserted that the only described example meets the limitations of what is actually being claimed, i.e. that it is a novel embodiment of what is claimed which includes the negative limitation. Second, the analogy is a false one because the requirements for proper rejections under 35 USC 101 and 35 USC 112, first paragraph are very different. The situation described by the applicant does not concern written description because unlike in the instant case, the novel chemical compounds that the applicant refers to are not defined as everything possible within certain parameters except for that which is present in nature. Such a claim would get a written description rejection like in the instant case. A rejection under 35 USC 101 requires some evidence or reasoning that the claimed product is present in nature. A rejection under 35 USC 112, first paragraph requires something quite different, presentation of evidence or reasoning that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor s , at the time the application was filed, had possession of the claimed invention. Again, the examiner respectfully submits that an invention defined by a negative exclusion must logically contain a description of that negative exclusion so as to convey to one of skill in the art that the inventors had possession of the claimed invention which in the instant case is defined by the negative limitation. No one of skill in the art could possibly believe that anyone has possession of a genus of nucleic acids encoding a chimeric protein which excludes certain types of proteins present in nature because one of skill in the art would readily realize that no one could possibly know what nucleic acids meet the claim limitations. Without knowing what nucleic acids meet the claim limitations, one of skill would not have a description of those nucleic acids that are being claimed.

The applicant also argues that the specification is clearly enabled as per in *Wands*. This argument (in the present rejection is not persuasive because it is directed to a different type of rejection. This argument is addressed in the arguments for the enablement rejection.

The applicant argues that "non-naturally occurring" and conceptually similar language are long accepted claim language

[illegible] raise description requirement. This argument is not persuasive for the following reasons. First, the negative limitations present in the claims are much more complex than simply "non-naturally occurring". The limitation is drawn to different specific occurrences that are excluded. Second, the applicant merely asserts that "non-naturally occurring" is long accepted without showing such usage and the context that it has been used in and how it relates to the current legal understanding as defined by current case law as it relates to the written description requirements for nucleic acid and protein sequences.

The applicant argues that the final guidelines for section 112 clearly state that there is a strong presumption that the specification as filed provides adequate written description support and that the PTO has the burden of showing why the applicant's evidence is insufficient and that the PTO should provide documentary evidence in support of the finding. The applicant does recognize that technical reasoning may support the finding when the technical line of reasoning relates to fact finding regarding possession of the invention. The applicant's argument is not persuasive for the following reasons. With regard to the strong presumption of adequate written description,

this is stated in the guidelines, but it is immediately followed by the following statements: "However, the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." This section goes on to state: "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process." It is the examiner's argument that because the claimed invention is defined by a negative limitation that clearly has not been described or is known to one skilled in the art, then the presumption of adequate written description is certainly overcome. The applicant actually did not present evidence of written description because the specification does not assert that even the one example of a method of making and encoding a chimeric protein actually meets the claim

limitations. The applicant's arguments do not present any other evidence of any sort showing written description for the claimed invention. The reasoning, including the facts concerning the nature of the art with regard to knowledge in the art regarding protein sequences, is set forth above and provide the prima facie case of lack of written description.

The applicant cites case law, Dickinson v. Zurko, but fails to show how it applies to the specifics of the instant written description rejection, merely stating a conclusion that the rejection is not supported by substantial evidence. This argument is not persuasive because arguments based only on conclusions without pointing out the specifics of the rejection which are defective are not persuasive. The reasoning that supports the rejection based upon lack of written description is clearly set forth, which rejection is in compliance with the current procedures as outlined in the Federal Register notice that the applicant cited and which follow the reasoning set forth in the most recent case law regarding written description of nucleic acid and protein sequences.

Therefore, in light of all available evidence, including the rejection set forth above and in the previous Office Action, the applicant's arguments, and the arguments set forth above, the

claims are still considered to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 41-70 and 72-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record set forth in Paper No. 33, mailed 9/21/00 and repeated below. Applicants' arguments filed 3/23/01 have been fully considered but they are not deemed to be persuasive.

The claimed invention is drawn to a nucleic acid and its use, the nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein the two nucleic acid binding domains do not occur in the same protein in nature, do not occur in the same

protein in nature in the order in which they are present in the chimeric protein, or do not occur in nature with the same spacing that is present in the chimeric protein.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claim. The most relevant Wands factors for evaluating the enablement of the instant rejection are discussed below.

The nature of the invention is complex because the exclusion conditions that form a limitation of the claimed nucleic acids and methods is complex, that such a combination of nucleic acid binding domains is not present in nature, nature being hugely complex. There are a limitless number of genes encoding different proteins in nature, especially including natural recombinants of those genes which resulted from a fusion between genes encoding different proteins, including different DNA binding proteins, which may result in natural chimeric nucleic acids as claimed (excluding the not present in nature part of the

claim limitations. An example of such natural fusions that occurs in nature are chromosomal breakpoint mutations, some of which involve DNA binding proteins.

The nucleic acids which meet the claimed limitations are highly unpredictable because for any given nucleic acid, all of the natural nucleic acids that exist in the natural world must be empirically determined and their sequences searched in order to determine whether the particular nucleic acid is encompassed by the claims or not. Without doing this, it is impossible to predict for any given combination of nucleic acid binding domains in a chimeric protein encoded by a nucleic acid, whether the nucleic acid meets all of the claim limitations, including the exclusions.

The amount of guidance is slight because both the art and the specification fail to teach even a small fraction of all possible sequences that any given nucleic acid must be compared to in order to determine whether that nucleic acid exists in nature or not.

Neither the art nor the specification teaches a working example of the claimed invention because neither the art nor the specification teaches a nucleic acid that definitively meets the

claim limitations, that the combination of nucleic acid binding [illegible] does not exist in nature.

In order to practice the claimed invention, one skilled in the art would have to envision an embodiment of the claimed invention, make it, test it in order to see whether it is functional in binding a composite DNA binding site, and if it does, then one skilled in the art would have to determine the nucleotide sequence of all genes that exist in nature, including mutant genes, and then compare the functional nucleic acid with all natural gene sequences in order to determine whether or not the nucleic acid is present in nature or not, and if it is not present in nature, then it is one functional embodiment that meets the claim limitations, out of the broad scope as claimed. This would require an absolutely enormous amount of experimentation because the nucleotide sequences of all natural genes, including all natural gene mutations would have to be determined in order to determine whether any particular nucleic acid meets the claim limitations. This amount of experimentation could not be accomplished in less than an infinite amount of time to practice even only one embodiment, which would be considered to be undue to practice the invention as broadly claimed.

Response to Arguments

The applicants argue that they are unaware of any legal [illegible] for enablement which requires that the practitioner of the claimed invention must be able to establish novelty of any particular embodiment covered by the claims. This argument is not persuasive for the following reasons. Rejections under 35 USC 112, first paragraph for lack of enablement are proper when the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (Underlining added by the examiner for emphasis.) In order to make a claimed invention, the [illegible] of skill in the art by necessity must determine whether an embodiment that may be the invention a particular nucleic acid in this case that is made meets the claim limitations. If the nucleic acid does not meet the claim limitations (i.e., is excluded on the basis of the negative exclusion , then that nucleic acid is not one that can be used when the claimed invention is used. If the nucleic acid meets the claim limitations, including the negative limitation, then that nucleic acid is one that can be used as an embodiment of the claimed invention, when one of skill in the art practices the claimed

invention. In the instant case, because the claimed invention includes the negative limitation which specifically excludes different combinations of nucleic acid binding domains that are present in the same protein in nature, one of skill in the art must be able to determine whether or not a particular combination of nucleic acid binding domains is present in nature or not before he makes the embodiment for use. Without this knowledge, it is impossible for one of skill in the art to clearly make an embodiment that meets the claim limitations because it can never be shown that any particular embodiment actually meets the claim limitations. Again, it is not that it is required that the practitioner of the claimed invention must be able to establish novelty of any particular embodiment covered by the claims. Instead, the specification must teach one of skill in the art how to make the claimed invention, and, in the instant case, one of skill in the art must be able to make a nucleic acid which has the negative limitation as claimed. Clearly, neither the art nor the specification provides teachings that would allow one of skill in the art to exclude the nucleic acids that encode the proteins as claimed, leaving only the claimed nucleic acids. This would result in a failure to make the claimed invention because only those nucleic acids that meet the negative

limitation conditions are those that are encompassed by the invention.

The applicant also argues (in the remarks concerning the written description rejection) that the specification is clearly enabled as per in *Wands*. However, the applicant failed to address the particulars of the enablement rejection which discusses how the *Wands* factors apply in the instant case. Arguments which merely state a conclusion without addressing the reasons for the conclusion and which fail to address the particulars of a reasoned argument against that conclusion, are simply not persuasive.

Therefore, in light of all available evidence, including the rejection set forth above and in the previous Office Action, the applicant's arguments, and the arguments set forth above, the claims are stilled considered to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-70, 72, 89-92, 94-95, and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW) in view of Mitchel et al (S), Harrison (T) and Schultz (U). This rejection is maintained for reasons of record set forth in Paper

No. 23, mailed 11/9/98, Paper No. 27, mailed 8/4/99, and Paper No. 33, mailed 9/21/00 and repeated below. Applicants' arguments filed 3/23/01 have been fully considered but they are not deemed to be persuasive.

Park et al teach a general strategy for designing proteins to recognize specific DNA-binding sites: this strategy is to select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together via a short peptide with a cysteine crosslink in a way compatible with each peptide being able to bind to its own DNA segment. This technique creates a protein that recognizes the composite site page 9094, column 1). This reference also teaches that use of the Gly-Gly-Cys linker is not essential in the design, that the cysteine can be replaced and a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made page 9095, column 2). The design is not limited to v-Jun. Any protein or other molecule that recognizes a specific DNA sequence by binding along the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form [illegible] target-binding sites for designing binding proteins. Of course, the segments of these proteins should be designed so

that the intramolecular interactions are not so strong as to [illegible] with binding to the DNA (pages 9095-9096). Park et al. also teach that the strategy is not limited to two arms and that they could have stitched together three, four, or more arms with appropriate linkers to design proteins that would recognize DNA sequences with 15, 20, or 25 bp (page 9095, column 2).

Park et al do not teach to specifically use the DNA-binding domains from distinct families of nucleic acid binding domains, use of specific types of domains such as zinc-finger domains.

Mitchell et al teach that different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation domains (page 372, column 2). This reference teaches zinc-finger domains, homeodomains, helix-turn-helix domains, steroid hormone receptor domains, leucine zipper domains, etc (pages 372-373). Various types of separable activation domains are also taught: acidic domains that can form an amphipathic alpha-helical structure, glutamine-rich domain, and proline-rich domain (pages [illegible]).

Harrison teaches that many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that they

are independent folded units. Many different DNA-binding domains are taught, including HTH, homeodomains, different types of zinc-finger domains, steroid receptor DA binding domains, etc. Representative proteins having the domains, such as Sifler, etc are also taught and referenced (page 718).

Schultz teaches that enzymes can be created by adding or replacing entire binding or catalytic domains to generate hybrid enzymes with novel specificities. Selective fusion of nucleic acid-specific binding domains may produce sequence-specific DNA or RNA cleaving enzymes (page 431, column 1). This reference teaches that tailor-made enzymes have applications in chemistry, biology and medicine.

It would have been obvious to one of skill in the art at the time the invention was made to use the various DNA binding domains, activation domains, and cleavage domains, including heterologous ones, taught by Mitchell et al, Harrison, and Schultz in the general strategy for designing proteins to recognize specific DNA-binding sites taught by Park et al because Park et al teach that it is within the ordinary skill in the art to stitch the DNA binding domains together from any proteins that recognize a specific DNA sequence by binding along the major groove, to recognize a composite site and Mitchell et al,

Harrison, and Schultz teach such domains that can be functionally separated and recombined with other domains. One would have been motivated to do so for the expected benefit of creating a protein that recognizes the composite site, thereby increasing the specificity of the chimeric protein, as taught by Park et al, and creating hybrid enzymes with novel specificities that have applications in chemistry, biology and medicine as taught by Schultz. Absent evidence to the contrary, there would have been a reasonable expectation of success that the domains taught by Mitchell et al and Harrison could be combined with each other to create a protein that recognizes a composite binding site as taught by Parks et al.

With regard to making a nucleic acid and vector comprising the nucleic acid which encodes the chimeric protein, it would have been obvious to do so because Parks et al teach that a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made, instead of using a synthetic linker, and thus it would have been obvious to make a nucleic acid that encodes this protein and place the nucleic acid in a vector to express the protein, because such a way of making a mutated, recombinant protein is and was well known in the art.

With regard to the use of any specific domain or combinations of domains recited in the claims, it would have been obvious to make any of the recited combinations because the recited domains are all taught in the cited references or are and were well known in the art, and Parks et al teach that any combination of domains can be used, which would include heterologous ones.

With regard to the inclusion of an activation domain in the chimeric protein, it would have been obvious to do so because the cited references teach that the activation domain are separate from the DNA binding domains and thus can be included. One would have been motivated to do so for the expected benefit of making a transcriptional activation protein that binds to a more specific composite site, as taught by Parks et al.

With regard to separating the domains by one or more amino acids in the chimeric protein, it would have been obvious to do so because Parks et al teach that the domains can be separated by a linker.

With regard to including an additional 'third' nucleic acid binding domain, it would have been obvious because Park et al teach that more domains can be added, resulting in binding to a larger composite DNA binding site.

Response to Arguments

The applicant argues that it is plain that in its broadest sense Park et al is still limited to the use of cross-linking agents to generate chimeric DNA binding proteins from discontinuous polypeptide fragments because this reference teaches covalent stitching together of DNA-binding proteins to form a cysteine-crosslinked composite protein, and that the disclosure may be a general strategy for designing cysteine-crosslinked protein composites, but it does not in any way disclose the possibility of or suggest the desirability of designing making or using nucleic acids. This argument is not persuasive for the following reasons. First, the applicant is completely ignoring a part of the teaching of Park et al upon which the instant rejection rests which was clearly set forth above and in the previous Office Actions. Park et al specifically teaches that cysteine crosslinking is not essential for the design and that a continuous protein that recognizes a predictable site can be made: "Summarizing, we have designed a protein stitched together from segments derived from the natural protein to recognize a specific DNA-binding site, and we have established specific binding of the designed protein to this site. Note that use of the Gly-Gly-Cys linker is not essential

in the design. We could just as well replace the cysteine and [illegible] about [illegible]-amino acid protein that still retains a predictable site [illegible]." page 9795, column 2, beginning of the first full paragraph". This passage clearly shows that Park et al contemplated more than just cysteine-crosslinked proteins that are designed to bind to a specific DNA sequence. This reference explicitly states that the protein can be designed as a continuous protein. Second, although Park et al does not specifically teach that the continuous about 71 amino acid protein that the reference refers to may be made from a nucleic acid sequence which encodes it, the instant rejection does not rely upon Park et al alone to teach that a nucleic acid sequence should be made that encodes that type of protein. Making a mutated, recombinant protein by making a nucleic acid sequence that encodes the protein and placing the nucleic acid in a vector to express the protein is and was extremely well known in the art. This technology has been at the very heart of the entire biotechnology industry for decades and clearly is obvious to one of ordinary skill in the art! Once it is suggested to one of ordinary skill in the art that a protein be made, it is immediately very obvious to make a nucleic acid sequence encoding the protein and express it from a vector. The applicant has not

challenges this specific part of the obviousness argument, that since Park et al teaches making the continuous protein that binds a specific DNA sequence, it would have been obvious to make a nucleic acid sequence encoding the protein and expressing it. However, as further evidence that this is and was very well known, one merely needs to look to the teachings of Gossen et al which is a part of the rejection under 103 at of claims 40-71 and 73-98 (repeated below), which teaches a nucleotide molecule coding for a chimeric transactivator fusion protein. This reference clearly teaches expressing chimeric transcription factor proteins from nucleic acid sequences encoding them.

The applicant also argues that the Examiner fails to demonstrate how Park et al bridges the gap between the claimed invention and the deficiencies which the Examiner admits for the remaining references, and that absent a suggestion for the asserted combination in any of the references themselves, the combination of these references is itself legally impressible with respect to maintaining a rejection for obviousness. This argument is not persuasive because what makes the combination of cited references obvious was clearly set forth in the previous Office Actions and repeated in the instant Office Action. How the remaining references absent Park et al and what is and was

well known in the art remedy deficiencies of Park et al is clearly set forth in specific detail not addressed by the applicant in his instant argument. The applicant has not addressed the particulars of the step by step basis for obviousness that was set forth by pointing out the specific deficiencies of one or more parts of the obviousness argument/rejection. The applicant merely states that the Examiner has failed to demonstrate obviousness. This type of argument, which lacks arguments drawn to why particular parts of the obviousness rejection are deficient, is not persuasive. Instead of repeating the rejections which have already been set forth in their entirety, the applicant is directed to the rejections themselves which has all pertinent parts of the Graham v. Deere analysis clearly set forth.

Therefore, in light of all available evidence, including the rejection set forth above and in the previous Office Actions, the applicant's arguments, and the arguments set forth above and in the previous Office Actions, the claimed invention is still considered to have been obvious, and the rejection of the claims under 35 USC 103(a) is properly maintained.

Claims 41-71 and 73-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) as applied to claims 40-71 above, and further in view of Gossen et al (A). This rejection is maintained for reasons of record set forth in Paper No. 23, mailed 11/9/98, Paper No. 27, mailed 8/4/99, and Paper No. 33, mailed 9/21/00 and repeated below. Applicants' arguments filed 3/23/01 have been fully considered but they are not deemed to be persuasive.

The teachings of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) are cited above and applied as before. These references do not specifically teach placing the nucleic acid encoding the chimeric protein into a vector in which the expression of the chimeric protein is under the control of a promoter permitting gene expression in eukaryotic cells, a kit comprising the nucleic acid encoding the chimeric protein and a gene operably linked to the composite binding site, use of the chimeric protein for modulating expression of a gene in a cell comprising modulating expression of the chimeric protein in a cell which includes a gene operably linked to the composite binding site, and a method of making a cell for use in the claimed expression method.

Gossen et al teach a nucleotide molecule coding for a chimeric transactivator fusion protein comprising a DNA binding domain (tet repressor binding domain) and a transactivation domain (such as VP16 of HSV). A negative system, comprising a repressor domain, is also taught (column 2). A second nucleic acid is taught coding for a heterologous protein which is operably linked to a tet operator (the binding site for the DNA binding domain). A method to regulate gene expression by cultivating the eukaryotic cell comprising the nucleic acid vectors in a medium comprising tet is also taught, as is a kit comprising the nucleic acids (abstract; columns 1-3). A method of making such eukaryotic cells by transfecting the nucleic acids into the cells is taught (columns 3, 9). This reference also teaches that it is desired to create regulatory systems that do not rely on endogenous control elements (column 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a transcriptional regulatory system from the DNA encoding a chimeric transactivation protein made obvious by the teachings of Park et al (AM2), Mitchel et al (S), Harrison (T) and Schultz (U), using the method taught by Gossen et al because Gossen et al teach that it is within the ordinary skill in the art to make a nucleic acid

vector that encodes a chimeric transactivator fusion protein under the control of a promoter active in eukaryotic cells, a nucleic acid encoding a heterologous protein operably linked to a regulator binding site that the chimeric protein binds to, place the nucleic acids in a eukaryotic cell, regulate the expression of the chimeric protein, thereby regulating expression of the heterologous protein, and the other cited references teach a chimeric fusion transactivator protein that could be used to regulate the expression of genes in a similar fashion as that taught by Gossen et al. One would have been motivated to do so for the expected benefit of making regulatory systems that do not rely on endogenous control elements, the desirability of which is taught by Gossen et al. Absent evidence to the contrary, there would have been a reasonable expectation of success that the chimeric protein encoding DNA taught by the other cited references could be used to make a new, non-endogenous element regulatory system using the teachings of Gossen et al.

Response to Arguments

The applicant's arguments as they apply to the instant rejection were addressed above and all counter-arguments apply

equally to this rejection and thus the instant rejection under 35 USC 103(a) is maintained for the same reasons as the rejection set forth above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official

Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning missing attachments or other minor formalities of this communication should be directed to the patent analyst, Zeta Adams, whose telephone number is (703) 305-3291.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Richard Schwartz, can be reached on (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is 703 308-0196.

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

June 3, 2001